Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 1640

www.rsc.org/greenchem

COMMUNICATION

Highly efficient Ag(I)-catalyzed regioselective tandem synthesis of diversely substituted quinoxalines and benzimidazoles in water†

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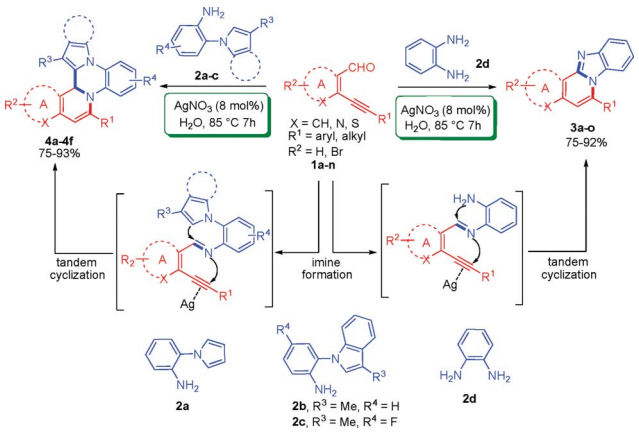
Received 31st March 2011, Accepted 9th May 2011
DOI: 10.1039/c1gc15346c

A green and operationally simple approach for the diverse synthesis of fused quinoxalines and benzimidazoles from *o*-alkynylaldehydes and amines having an *N*-tethered nucleophile using Ag(I) as the catalyst in water, is described. The X-ray crystallographic studies confirmed the proposed mechanistic pathway and the cyclized product.

Rapid advances in medicinal chemistry continue to underscore the need of practical routes for the synthesis of heterocycles as the majority of drug-like compounds contain heterocycles at their core.[1] Recently, transition metal-catalyzed tandem processes provided a promising method towards this aim which enabled the efficient conversion of simple starting materials to complex molecules in an repetitive manner.[2] Among the various transition metals employed in tandem cyclizations, silver-catalyzed cyclizations have gained considerable attention because of their ability to activate various π-systems at mild conditions and at low-catalyst loading.[3]

As a privileged fragment, isoquinolines are present in a variety of natural products and in numerous pharmaceutically important compounds.[4] Quinoxalines are an important class of benzoheterocycles[5a] that constitute the building blocks of some organic semiconductors[5b] and a wide range of pharmacologically active compounds including anticancer[5c] and antimicrobial agents.[5c,5d] So the molecular skeleton which integrates isoquinoline as well as quinoxaline moieties might possess properties of both and enhance the activity. Similarly, isoquinoline-fused benzimidazoles have attracted considerable interest due to their outstanding biological activities, such as anti-HIV-1, anticancer, antimicrobial and antifungal properties.[6] Thus, the development of novel and efficient routes for rapid access to such functionalized isoquinolines under mild conditions is of high demand.

In this regard, some progress has been accomplished *via* tandem nucleophilic addition and electrophilic cyclization using *o*-alkynylbenzaldehyde, amine and various carbon pronucleophiles in the absence[7] or in the presence of various alkynophilic Lewis acid catalysts.[8] To the best of our knowledge, tandem synthesis of pyrrolo and indolo fused quinoxaline and benzimidazoles from *ortho*-alkynylaldehydes in water has not been explored. Most notably, reactions of water insoluble organic compounds taking place in aqueous suspension ("on water") are gaining considerable attention due to their high efficiency and straightforward synthetic protocol.[9] Water, in contrast to common organic reaction media, is an environment friendly, cheap, imflammable reaction medium which has often had an unprecedented effect on the rate and selectivity of organic reactions through hydrophobic interactions and enrichment of organic substrates in the local hydrophobic environment.[10] As a part of our ongoing efforts to synthesize *N*-heterocycles,[11] we herein, present our findings on the synthesis of isoquinolino[2,1-*a*]pyrrolo/indolo[2,1-*c*]quinoxalines and benzimidazo[2,1-*a*]isoquinolines *via* a $AgNO_3$-catalyzed one-pot tandem sequence in water using *o*-alkynylaldehydes and amines with tethered nucleophiles (Scheme 1). This cascade strategy involves the formation of two new carbon–nitrogen bonds and one new carbon–carbon bond thereby leading to the formation of two heterocyclic rings in one-pot giving fused polycyclic heterocycles.



Scheme 1 Tandem synthesis of fused quinoxalines and benzimidazoles.

For the initial experiments, we selected 2-phenylethynyl benzaldehyde (**1a**) and 2-(1*H*-pyrrol-1-yl)aniline (**2a**) as model

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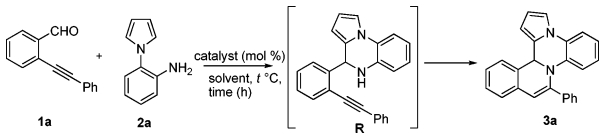
† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for target compounds. CCDC reference number for compound **3a** is 818980 and for compound **R** is 819358. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1gc15346c

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Conditions			Yield (%)[c]	
		Solvent	T °C	Time (h)	**R**	**3a**
1	$PdCl_2$	CH_2Cl_2	25	12	55	0[b]
2	$Pd(OAc)_2$	CH_2Cl_2	25	12	60	0[b]
3	CuI	CH_2Cl_2	25	12	48	5[b]
4	AgOAc	CH_2Cl_2	25	12	40	30[b]
5	AgI	CH_2Cl_2	25	12	25	0[b]
6	AgOTf	CH_2Cl_2	25	12	35	52[b]
7	$AgNO_3$	CH_2Cl_2	25	12	30	65[b]
8	$AgNO_3$	CH_2Cl_2	25	10	25	70
9	$AgNO_3$	THF	80	12	30	60
10	$AgNO_3$	Toluene	80	10	25	67
11	$AgNO_3$	EtOH	80	10	55	25
12	**$AgNO_3$**	**H_2O**	**85**	**7**	**0**	**92**
13	$AgNO_3$	H_2O	85	10	0	92
14	$AgNO_3$	H_2O	85	10	25	70[b]
15	—	H_2O	85	10	—	—

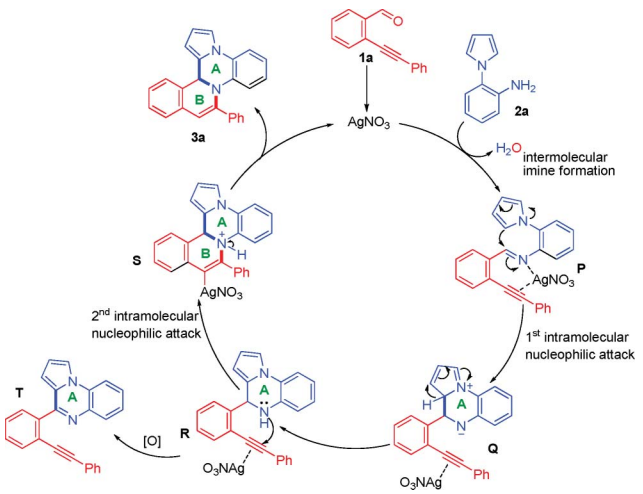
[a] The reactions were performed using *o*-alkynylaldehyde **1a** (0.50 mmol), amine **2a** (0.50 mmol), 8.0 mol% of $AgNO_3$ in 2.0 mL of solvent unless otherwise noted. [b] 5.0 mol% of $AgNO_3$ was used. [c] Yield of isolated product.

substrates (Table 1). When 5.0 mol% of $PdCl_2$, $Pd(OAc)_2$ were used as catalysts in CH_2Cl_2, the reaction was stopped at the formation of intermediate **R** and no formation of the desired product **3a** was observed in 12 h (entries 1–2). Similar results were obtained when other transition metal-catalysts like CuI, AgOAc, AgI were used (entries 3–5). When AgOTf was used, it provided the product **3a** in only 52% yield along with 35% of **R** in 12 h at rt (entry 6). When 5 mol% of $AgNO_3$ was used in CH_2Cl_2, it led to the formation of **3a** in 65% yield in 12 h (entry 7). However, when 8.0 mol% $AgNO_3$ was used, it resulted the formation of product **3a** in 70% yield in 10 h (entry 8). Screening different solvents did not provide the desired product **3a** in good yields (entries 9–11). Surprisingly, when water was employed as a solvent with 8.0 mol% of $AgNO_3$, it provided the formation of **3a** in 92% yield at 85 °C in 7 h (entry 12). It is notable that vigorous stirring was required to promote the reaction, most likely by increasing the area of contact between the organic and aqueous phase.[9a,12] It was noticed that when reaction duration was increased from 7 to 10 h, it had no effect on the yield of the product **3a** (entry 13). Reducing the amount of $AgNO_3$ from 8.0 to 5.0 mol% adversely decreased the yield of **3a** to 70% (entry 14). However, in the absence of catalyst, reactants remained unchanged during the course of the reaction (entry 15).

Under the optimized reaction conditions, we then examined the scope of this reaction. As shown in Table 2, the reaction was tolerant towards a variety of *o*-alkynylaldehydes **1** bearing different alkynyl substituents R^1. When an electron-donating group was used as R^1, then reaction was well implemented to form intriguing cyclized products **3a–b** in 92–94% yields (entries 1–2). When an electron-rich heteroaromatic moiety like thiophene was used as R^1, it afforded the formation of product **3c** in 93% yield (entry 3). A comparable yield of **3d** was obtained when the bromo substituted substrate **1d** was used (entry 4). Products **3e–g** were obtained in 75, 78, 75% yields respectively when *n*-butyl, cyclohexyl and trimethylsilyl were employed as R^1 (entries 5–7). Furthermore, when a heteroaromatic nucleus was introduced in substrates **1h–j**, the reaction proceeded well and provided the desired fused scaffolds **3h–j** in 85–92% yields (entries 8–10). When 2-(3-methyl-1*H*-indol-1-yl)aniline **2b** was employed as the amine, the reaction proceeded well and products **3k–o** were obtained in 78–93% yields (entries 11–15). When electron-rich aromatic, heteroaromatic, substituents were used as R^1 and a fluoro group used as R^4, reaction proceeded well and provided the corresponding desired fused compounds **3l–n** in 90–93% yield (entries 12–14). A comparative decrease in yield was observed in the case of an alicyclic substituent R^1 (entry 15).

We then further employed the same protocol to examine its scope for the reaction of benzene-1,2-diamine **2d** with functionally varied *o*-alkynylaldehydes **1** (Table 3). Reaction proceeded well with aromatic R^1 group, which provided the fused benzimidazole scaffolds **4a–b** in 88 and 92% yield respectively (entries 1–2). The reaction well accommodated the heteroaromatic nucleus like pyridine, benzothiophene, quinoline coupled with aromatic, alicyclic, alkyl substituents respectively; as *o*-alkynylaldehydes **1i**, **1l**, **1m–n** which provided the desired polycyclic heteroaromatic products **4c–f** in 75–90% yield (entries 3–6).

With these observations in hand, a plausible mechanism is proposed (Scheme 2). **1a** and **2a** generate the condensation species **P** which upon activation by $AgNO_3$ results in the nucleophilic attack from the C-2 position of the pyrrole ring onto the imine carbon to form **Q** which after subsequent aromatization affords species **R**. π-Complexation between the alkyne and Ag(I) renders a regioselective 2nd intramolecular attack of nucleophilic NH onto the alkyne to form intermediate **S**, which after subsequent deprotonation leads to the formation of cyclized product **3a**.

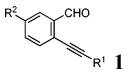
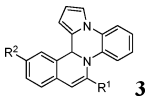
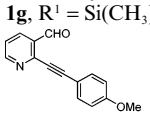
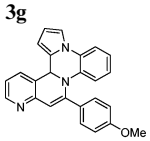
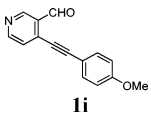
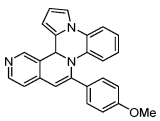
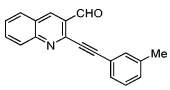
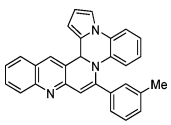
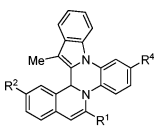


Scheme 2 Plausible mechanism.

The regioselective formation of **3a** was confirmed by X-ray crystallography (Fig. 1).

To support the proposed mechanism, we monitored the progress of the reaction between **1a** and **2a** with 5 mol% $AgNO_3$ in water at 85 °C. After 3 h, we observed the formation of intermediate **R** as a major spot from the TLC along with its

Table 2 Tandem synthesis of fused quinoxalines[a]

Entry	Substrate	Amine	Product	Yield (%)[b]
	 **1**	**2a**	 **3**	
1	**1a**, R^1 = Ph, R^2 = H	**2a**	**3a**	92
2	**1b**, R^1 = 4-OMePh, R^2 = H	**2a**	**3b**	94
3	**1c**, R^1 = 3-thienyl, R^2 = H	**2a**	**3c**	93
4	**1d**, R^1 = Ph, R^2 = Br	**2a**	**3d**	85
5	**1e**, R^1 = $C(CH_3)_3$, R^2 = H	**2a**	**3e**	75
6	**1f**, R^1 = cyclohexyl, R^2 = H	**2a**	**3f**	78
7	**1g**, R^1 = $Si(CH_3)_3$, R^2 = H	**2a**	**3g**	75
8	 **1h**	**2a**	 **3h**	92
9	 **1i**	**2a**	 **3i**	89
10	 **1j**	**2a**	 **3j**	85
	1	**2**	 **3**	
11	**1a**, R^1 = Ph, R^2 = H	**2b** R^4 = H	**3k**	88
12	**1k**, R^1 = *p*-*t*-bu C_6H_4, R^2 = H	**2b** R^4 = H	**3l**	90
13	**1b**, R^1 = *p*-OMe-C_6H_4, R^2 = H	**2c** R^4 = F	**3m**	93
14	**1c**, R^1 = 3-thienyl, R^2 = H	**2c** R^4 = F	**3n**	91
15	**1f**, R^1 = cyclohexyl, R^2 = H	**2b** R^4 = H	**3o**	78

[a] The reactions were performed using *o*-alkynylaldehyde **1** (0.50 mmol), amine **2** (0.50 mmol), 8.0 mol % of $AgNO_3$ in 2.0 mL of H_2O at 85 °C for 7 h, unless otherwise noted. [b] Yield of isolated product.

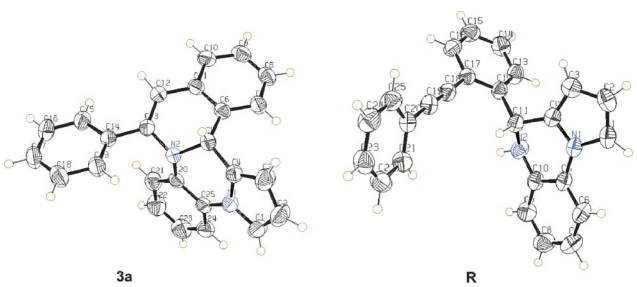
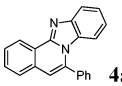
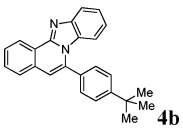
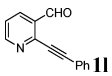
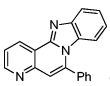
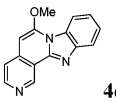
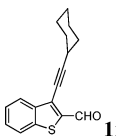
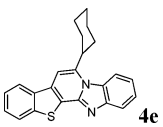
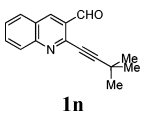
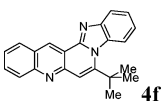


Fig. 1 X-Ray crystallographic structure of **3a** and **R** (ORTEP drawing).

oxidized form **T**. Both were then isolated and characterized by NMR. Intermediate **R** was finally confirmed by X-ray crystallography (Fig. 1). Isolation of intermediate **R** clearly confirms that the reaction proceeds *via* the formation of the heterocyclic ring **A** first, *via* the nucleophilic attack from the pyrrole ring to imine carbon and not the formation of ring **B** which would occur *via* the formation of isoquinolinium intermediate.[13]

In conclusion, we have developed an environmentally benign Ag(I)-catalyzed tandem protocol in water which provides a facile access to fused polycyclic quinoxalines and benzimidazoles in good to excellent yields with high regioselectivities and diversity. These atom economical transformations in water proceeded with high functional group tolerance. The proposed mechanistic pathway (sequential C–N, C–C and N–C) was confirmed by the X-ray crystallographic studies. Owing to the great diversity of the substitution pattern, this developed chemistry can be used for the generation of libraries of various heterocyclic systems. Further investigations in this area are currently under way and will be reported in due course.

Table 3 Tandem synthesis of fused benzimidazoles[a]

Entry	Substrate	Amine	Product	Yield(%)[b]
1	**1a**	**2d**	 **4a**	88
2	**1k**	**2d**	 **4b**	92
3	 **1l**	**2d**	 **4c**	89
4	**1i**	**2d**	 **4d**	90
5	 **1m**	**2d**	 **4e**	75
6	 **1n**	**2d**	 **4f**	84

[a] The reactions were performed using *o*-alkynylaldehyde **1** (0.50 mmol), amine **2d** (0.50 mmol), 8.0 mol% of $AgNO_3$ in 2.0 mL of H_2O at 85 °C for 7 h, unless otherwise noted. [b] Yield of isolated product.

Acknowledgements

We gratefully acknowledge the Department of Science and Technology (SR/S1/OC-66/2010) Govt. Of India for providing financial support and USIC, University of Delhi for providing instrumentation facilities. V.R. and T.A. are thankful to CSIR, New Delhi for a fellowship.

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